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Preparation of surface-modified stimuli-responsive polymeric membranes by plasma and ultraviolet grafting methods and their riboflavin permeation

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Acrylic monomers were grafted on the surface of commercial polyamide membranes using plasma polymerization and ultraviolet irradiation techniques. Graft reaction was confirmed by X-ray photoelectron spectra. Grafting yield increased with plasma and ultraviolet exposure time. Permeation of riboflavin through graft membranes was investigated. Poly(acrylic acid-*g*-amide) membranes showed a decrease in permeability of riboflavin at pH 4–5, while poly(methacrylic acid-*g*-amide) membranes exhibited decreased permeability at pH 6–7 regardless of the grafting methods. *N*-isopropylacrylamide-grafted polyamide membrane showed a temperature-dependent permeation of riboflavin.

(Keywords: stimuli-responsive membranes; plasma and u.v. grafting; permeability)

INTRODUCTION

Many researchers have reported on controlled drug delivery systems utilizing drugs loaded on a polymer matrix[1–18]. Drug delivery systems have received much attention because they can maximize the therapeutic effect by maintaining an effective drug concentration in the blood through zero-order release for a prolonged period of time. Among such systems, macromolecular drugs, polymeric membrane systems, polymer hydrogels and lipids have been suggested as effective tools for drug delivery. Recently, much attention has been paid to stimuli-responsive drug delivery systems. Stimuli include electricity[5,6], pH[7–10], glucose concentration[11–14] and temperature[15–18].

Iwata *et al.* reported on the graft polymerization of acrylamide and acrylic acid onto a polyethylene[19,20] and poly(vinylidene fluoride)[15] using a glow discharge technique. The bovine serum albumin filtration rate and ion transport rate were determined as a function of pH and ion concentration[15]. Osada *et al.*[21] grafted poly(methacrylic acid) onto a porous poly(vinyl alcohol) membrane using plasma treatment, and the ion transport, albumin and poly(ethylene glycol) permeation behaviours were studied. The poly(methacrylic acid)-grafted membrane showed a pH-dependent permeation behaviour. X-ray photoelectron spectroscopy (X.p.s.) was utilized to confirm the graft reaction. Recently, Ito *et al.*[22] reported on the water permeation through a porous polycarbonate membrane having poly(acrylic acid) on the membrane surface by pH and ionic strength. Uchida *et al.*[23] prepared ionic acrylic monomers on the surface of poly(ethylene terephthalate) using the u.v. irradiation method. We have reported on the grafting of acrylic monomers onto porous polyurethane for pH-sensitive membranes prepared by the chemical initiation method[24].

The aim of this study is to investigate the effective means of grafting acrylic functional monomers onto porous polymeric membranes. Grafting methods include the plasma and u.v. techniques. The acrylic monomers examined were acrylic acid, methacrylic acid and *N*-isopropylacrylamides. The first two monomers were known to be pH-sensitive[19–23] and the last one to be temperature-sensitive[15–17]. The effects of graft density on the permeability of riboflavin as a model drug were examined.

EXPERIMENTAL

Acrylic acid (AA) and methacrylic acid (MAA) (both from Junsei Chemical Co.) were used after vacuum distillation. *N*-isopropylacrylamide (NIPAm; Tokyo Kasei Chemical

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Co.) was used after recrystallization in hexane and toluene (40:60 vol%). Riboflavin (Junsei Chemical Co.) was used without any further treatment. Benzophenone (Aldrich Chemical Co.) was used as a photosensitizer after recrystallization in methanol. Porous polyamide membrane from Gelman Science Co. has 120 μm thickness, 0.2 μm pores and 20% porosity. It was used after cleaning in methanol.

For plasma polymerization, a bell-jar-type plasma reaction apparatus was used to accommodate acrylic monomers. The porous membrane was placed on the bottom electrode of the reaction apparatus. The reactor was evacuated to 50 mtorr. Then, a 50 W argon plasma was used for varying times (0, 3, 5 and 7 min). Treated polymer membrane was exposed immediately in the air and dipped into prepared 20 wt% monomer solution. After the reaction under nitrogen atmosphere at 60°C, it was dipped into distilled water at 50°C for 24 h to remove any residual monomers and homopolymers.

U.v. grafting was conducted using a 450 W u.v. lamp (Ace Glass Co.) and benzophenone as a photosensitizer to graft acrylic monomers onto porous polyamide membranes. Benzophenone (10 wt%) dissolved in monomer/methanol was dropped on the surface of the membrane followed by the reaction in nitrogen atmosphere for 30 min. Reacted membranes were rinsed several times with deionized water and methanol. Graft yield was calculated from the following equation:

$$\text{graft yield (\%)} = \frac{W_t - W_o}{W_o} \times 100$$

where W_0 and W_t represent the weight of the membrane before and after the graft reaction.

For the measurement of permeability of riboflavin, the permeation cell has two compartments of equal volume (100 ml). Each chamber was mechanically stirred at 750 rev min^{-1} to eliminate the boundary layer resistance. All measurements were made at 37°C in this study. One compartment of the cell was filled with phosphate buffer at pH 7.4, and the other side with a solution of riboflavin. Aliquots of the buffer solution were taken out after a given period of time. The u.v. absorbance of the solution was measured with a spectrophotometer (Spectronic 21, Milton Roy Co.) at 444 cm^{-1} wavelength to determine the concentration of riboflavin in the feed and in the permeate. The solute permeability coefficient P was calculated from the equation that was obtained from the mass balance equation[11].

The graft reaction of acrylic monomers was confirmed by X-ray photoelectron spectroscopy (Surface Spectrometer Inc., model 2803-S) using the Mg Kα-X line and 90° take-off angle. For plasma-treated membranes, the amount of peroxide formed on the surface was quantified with 1,1-diphenyl-2- picrylhydrazyl (DPPH). The reacted membrane was exposed in the air and dipped into the DPPH/toluene solution (1×10^{-4} mol l^{-1}) at 60°C for 2 h. The solution was quantified by observing the decrease in the absorption at 520 nm using the spectrophotometer.

RESULTS AND DISCUSSION

One of the advantages of the plasma polymerization technique was that the polymerization reaction was only limited to the surface of the membrane. After the plasma exposure, the membrane was taken out of the plasma reactor and was exposed in the air. At this stage peroxide was formed on the membrane surface. Upon dipping into the acrylic monomer solution, the graft reaction initiated very rapidly. The mechanism of this kind of reaction involves the generation of free radicals from the main chain of the polymer, the formation of peroxide upon air exposure, followed by the initiation and propagation of the acrylic monomers.

An increase of plasma exposure time from 3 to 7 min increases the amount of peroxide formed on the polyamide membrane surface as determined by DPPH.

X.p.s. spectra as shown in *Figure 1* confirmed the graft reaction. As summarized in *Table 1*, the area under the curves and the area ratio of N_{1s}/O_{1s} relatively decreased and O_{1s} peak area increased as the acrylic acid and

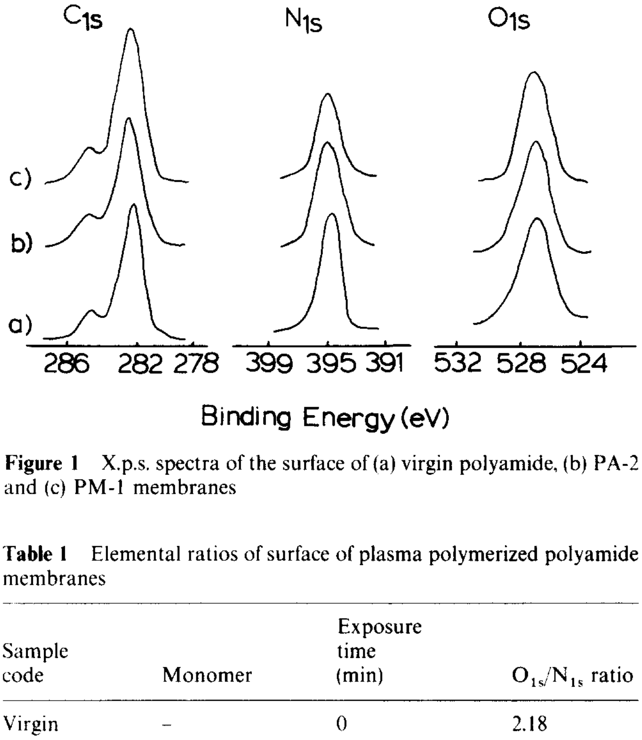

Figure 1 X.p.s. spectra of the surface of (a) virgin polyamide, (b) PA-2 and (c) PM-1 membranes

Table 1 Elemental ratios of surface of plasma polymerized polyamide membranes

Sample code	Monomer	Exposure time (min)	O_{1s}/N_{1s} ratio
Virgin	–	0	2.18
PA-1	AA	3	2.84
PA-2	AA	5	4.54
PA-3	AA	7	4.74
PM-1	MA	3	2.52
PM-2	MA	5	2.70
PM-3	MA	7	3.80

Table 2 Graft yield of membranes prepared by u.v. irradiation method

Sample	Monomer	Monomer ratio	Monomer conc.	Graft yield (%)
UA-1	AA	–	10	24.5
UA-2	AA	–	20	34.3
UA-3	AA	–	30	37.7
UM-1	MA	–	10	1.8
UM-2	MA	–	20	5.3
UM-3	MA	–	30	17.9
UI-1	NIPAm/Am	100/0	10	1.6
UI-2	NIPAm/Am	80/20	10	3.2
UI-3	NIPAm/Am	70/30	10	3.1

methacrylic acid were grafted, indicating the increase of grafting content with plasma exposure time. From the X.p.s. spectra of both front and back of the plasma-treated membrane, we see that the graft reaction only proceeds on the front side of the membrane.

The structures of u.v. graft membranes were confirmed by a.t.r.-*FT*i.r. spectra showing the absorption peak at 3300 and 1730 cm^{-1} due to the presence of carboxyl groups in both acrylic acid and methacrylic acid graft membranes. The graft yield of the polymer increased with the monomer concentration as can be seen in *Table 2*.

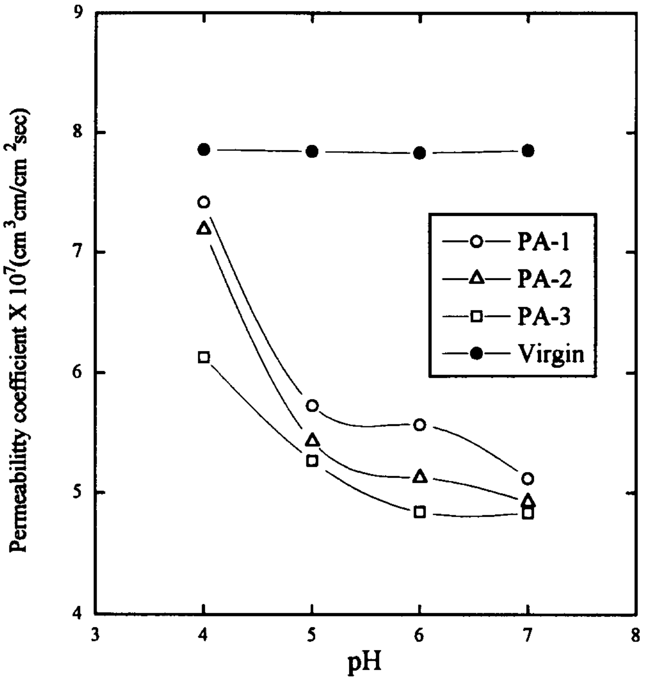

Figure 2 Effect of pH on the riboflavin permeation through PA membranes

For the virgin polyamide membrane, the permeability of riboflavin was constant as pH varies. However, as can be seen in *Figures 2* and *3*, poly(acrylic acid-*g*-amide) membrane showed the pH-dependent permeability of riboflavin, regardless of the grafting methods. Particularly at pH 4–5, these membranes showed a rapid decrease in permeability of riboflavin. The drastic drop in permeability at pH 4–5 can be explained from the fact that poly(acrylic acid) is an ionic polymer showing $pK_a = 4.8^{22,25}$, dissociates into carboxylate ions in methanol and basic solution, and exhibits extended conformations because of the ionic repulsion forces resulting in the decrease of the effective pore sizes as the solution is above $pK_a = 4.8$ solution range. In the lower pH range, the polymer chain forms a contracted conformation contributing to an increase in effective pore sizes and thus the decrease in solute permeability. PA-3 membrane treated for 7 min in the plasma reactor showed the smallest changes in permeability. This is attributed to the fact that there exists an optimum point in radical formation and the chain-growth radical reaction of acrylic monomers.

Poly(methacrylic acid-*g*-amide) membranes showed a drastic decrease in permeability at pH 6–7 (*Figures 4* and *5*). This result is related with $pK_a = 6.15^{22,26}$ for poly(methacrylic acid). As graft density increases, the permeability decreases. X.p.s. results also indicated that the (methacrylic acid)-*g*-polyamide membrane showed lower graft density than the (acrylic acid)-*g*-polyamide membrane. However, the change in permeability is more drastic in (methacrylic acid)-*g*-polyamide membrane than in (acrylic acid)-*g*-polyamide membrane. This result is in agreement with the previous results on the polyurethane graft membrane initiated by the chemical method[24]. The methyl group in methacrylic acid contributes to the hydrophobic interaction[27] and may form a more effective conformation for the permeation when contracted.

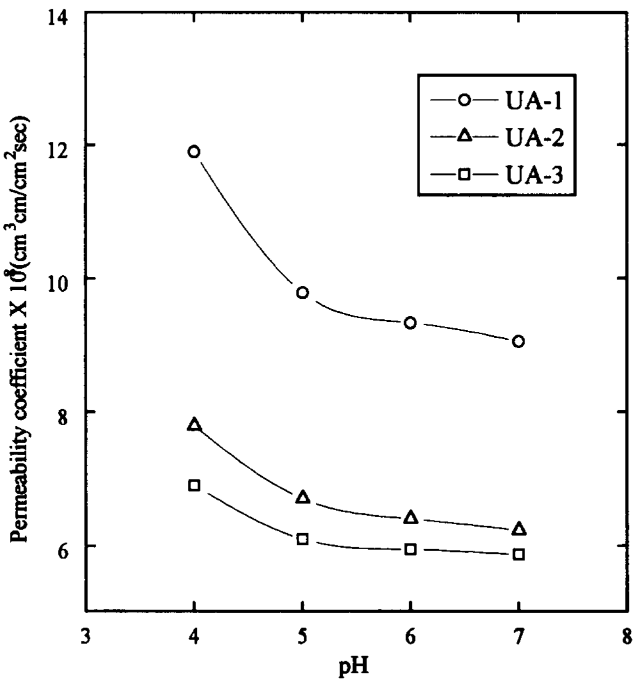

Figure 3 Effect of pH on the riboflavin permeation through UA membranes

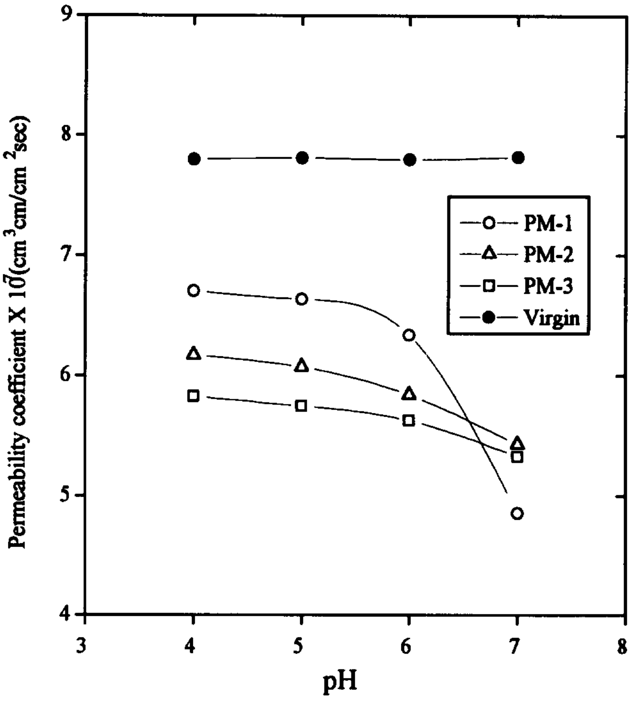

Figure 4 Effect of pH on the riboflavin permeation through PM membranes

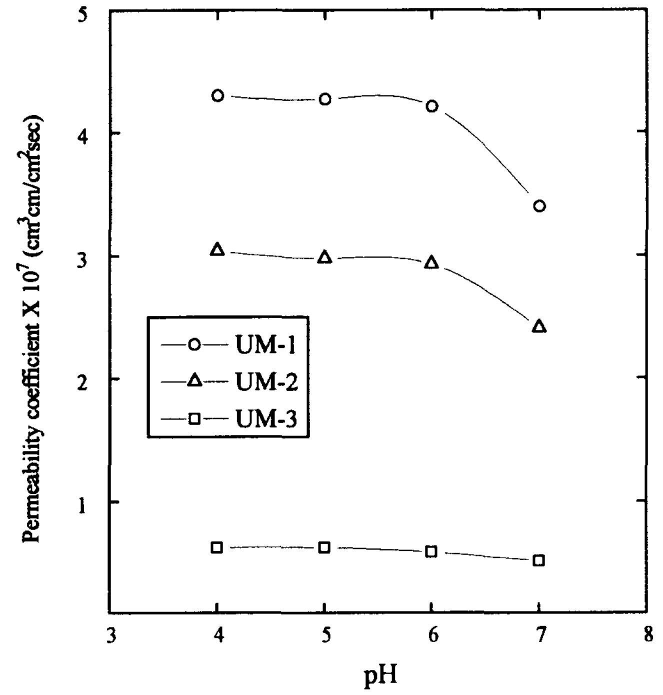

Figure 5 Effect of pH on the riboflavin permeation through UM membranes

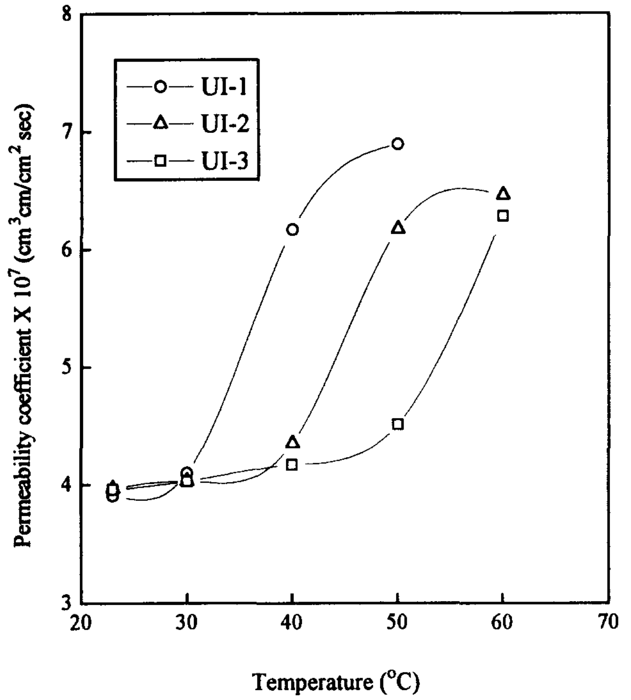

Figure 6 Effect of temperature on the riboflavin permeation through UI membranes

The above results show the possibility of controlling the pH region, in which the riboflavin permeability changes most sensitively with pH, by choosing the nature of the polymers to be grafted. This information is important in the design of a polyelectrolyte-grafted porous membranes for a drug delivery system under physiological conditions.

As NIPAm is grafted on the porous polyamide membrane using the u.v. grafting technique, the permeability changes with temperature rather than with pH (*Figure 6*). Poly(NIPAm)[15,16] is known to have a lower critical solution temperature (*LCST*) at around 31–33°C. Below *LCST*, poly(NIPAm) forms hydrogen bonds with water and exists in solution form. However, above *LCST*, inter- and intramolecular interaction in poly(NIPAm) is much stronger, resulting in an undissolved state. In this state, the hydrogen bonding between grafted poly(NIPAm) (UI-1) and water breaks down and the mobility of the polymer chain, inter- and intramolecular interaction as well as the hydrophobic interaction due to the presence of the alkyl groups in the polymer chain increases[23]. Grafted poly(NIPAm) chain shrinks, leading to enlargement of the effective pore size. In contrast to this, at lower *LCST*, the hydrophobic interaction is weakened and the hydrophilic interaction and hydrogen bonding between water and the polymer chain increase. Therefore, the hydration of water molecules that surround the polymer chain contributes to the extension of the polymer chain resulting in the shrinkage of the effective pore size and thus the smaller permeability.

UI-2 and UI-3 used the acrylamide as a comonomer with NIPAm. In this case, the transition temperature of permeability changes from 40°C to 50°C. According to Muller *et al.*[28], as the carbon in the alkyl chain in alkylacrylamide increased, the *LCST* decreased from 50°C. This result is explained by the fact that, as the length of the alkyl chain increases, the solubility of the polymer in water was lowered, leading to a drop in the *LCST*. Acrylamide homopolymer, which does not possess any alkyl chains, does not show the *LCST* at below 95°C. In the present study, hydrophilic acrylamide copolymerized with NIPAm on the surface of the polyamide membrane. Therefore, the hydrophilic interaction of the copolymer was enhanced, contributing to the increase in *LCST*.

These results led to the conclusion that both the acrylic acid and methacrylic acid graft polyamide membrane showed pH-dependent permeation behaviour regardless of the grafting methods. Acrylic acid graft polymer showed the transition in permeability at pH 4–5, while methacrylic acid graft polymer exhibited the change in permeability at pH 6–7. It was believed that the

Table 3 Comparison of pH sensitivity of membranes as a function of the graft methods

Initiation method	Sample	$P_{pH=4}/P_{pH=7}$[a]
Plasma	PA-1	1.33
	PA-2	1.47
	PA-3	1.05
	PM-1	1.41
	PM-2	1.15
	PM-3	1.10
U.v.	UA-1	1.30
	UA-2	1.24
	UA-3	1.17
	UM-1	1.30
	UM-2	1.25
	UM-3	1.25

[a] Ratio of permeability coefficient of riboflavin measured at pH = 4 and pH = 7

methyl group on the α-carbon in methacrylic acid contributed to the hydrophobic interaction, which may lead to the shrinkage of the effective pore size occurring in the pH range close to the neutral range. It was difficult to compare the absolute chain length as a function of the grafting methods because each technique has different conditions of preparation. Nevertheless, plasma-treated polymer membrane samples PA-1 and PM-1 showed the highest pH sensitivity as listed in *Table 3* determined solely by the ratio of the riboflavin permeability at pH = 4 and at pH = 7.

CONCLUSIONS

We prepared pH-sensitive polymer membranes by grafting acrylic monomers such as acrylic acid, methacrylic acid, NIPAm and acrylamide utilizing u.v. irradiation and plasma polymerization techniques. The change in permeability of the model drug, riboflavin, occurs at pH 4–5 and pH 6–7 for acrylic acid and methacrylic acid, respectively. In the present study, plasma polymerized membranes showed the more sensitive changes in permeability as a function of pH. For u.v. polymerized membranes, the excess monomer may have polymerized. This was supported by the lower permeability and the lower pH sensitivity of u.v. polymerized polymer membrane, compared with the plasma polymerized membranes. The graft density and the molecular weight of the solute influence the permeability and the transition of the membrane. Among the membrane samples, PA-1 and PM-1 showed the highest pH sensitivity. NIPAm and AAm grafted polymer membranes showed the temperature-dependent permeation behaviour of riboflavin. The transition temperature increased from around 30°C to 50°C depending on the amount of AAm added to the NIPAm reaction medium as a comonomer.

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